Complete Summary

GUIDELINE TITLE

Induction and adjuvant therapy for N2 non-small-cell lung cancer.

BIBLIOGRAPHIC SOURCE(S)

Gopal RS, Komaki RU, Bradley J, Gewanter RM, Movsas B, Rosenzweig KE, Thoms WW Jr, Weisenburger TH, Wolkov HB, Kaiser LR, Schiller JH, Mauch PM, Expert Panel on Radiation Oncology-Lung Work Group. Induction and adjuvant therapy for N2 non-small-cell lung cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2006. 16 p. [94 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Byhardt RW, Sause WT, Curran WJ, Fuller D, Graham MV, Ko B, Komaki R, Weisenburger TH, Kaiser LR, Leibel SA, Choi NC. Neoadjuvant therapy for marginally resectable (clinical N2), non-small cell lung cancer. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000 Jun;215(Suppl):1331-45.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

N2 non-small-cell lung cancer (NSCLC)

GUIDELINE CATEGORY

Treatment

CLINICAL SPECIALTY

Internal Medicine
Oncology
Pulmonary Medicine
Radiation Oncology
Radiology
Surgery

INTENDED USERS

Health Plans
Hospitals
Managed Care Organizations
Physicians
Utilization Management

GUIDELINE OBJECTIVE(S)

To evaluate the appropriateness of radiologic treatment procedures for patients with N2 non-small-cell lung cancer (NSCLC)

TARGET POPULATION

Patients with N2 non-small-cell lung cancer (NSCLC)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Radiation therapy alone
2. Surgery alone
3. Concurrent chemoradiation, then surgery
4. Concurrent definitive chemoradiation, no surgery
5. Neoadjuvant chemotherapy, then surgery
6. Sequential chemotherapy, then radiation, then surgery
7. Consideration of radiation therapy doses and technique

MAJOR OUTCOMES CONSIDERED

- Short-term, long-term, and recurrence-free survival rates
- Response rates (complete and partial) to induction chemotherapy
- Median and long-term survival time
- Operative mortality rate

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developer performed literature searches of peer-reviewed medical journals and the major applicable articles were identified and collected.

NUMBER OF SOURCE DOCUMENTS

The total number of source documents identified as the result of the literature search is not known.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Not Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not stated

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

One or two topic leaders within a panel assume the responsibility of developing an evidence table for each clinical condition, based on analysis of the current literature. These tables serve as a basis for developing a narrative specific to each clinical condition.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Since data available from existing scientific studies are usually insufficient for meta-analysis, broad-based consensus techniques are needed for reaching agreement in the formulation of the appropriateness criteria. The American College of Radiology (ACR) Appropriateness Criteria panels use a modified Delphi technique to arrive at consensus. Serial surveys are conducted by distributing questionnaires to consolidate expert opinions within each panel. These questionnaires are distributed to the participants along with the evidence table and narrative as developed by the topic leader(s). Questionnaires are completed by participants in their own professional setting without influence of the other members. Voting is conducted using a scoring system from 1-9, indicating the least to the most appropriate imaging examination or therapeutic procedure. The survey results are collected, tabulated in anonymous fashion, and redistributed after each round. A maximum of three rounds is conducted and opinions are unified to the highest degree possible. Eighty percent agreement is considered a consensus. This modified Delphi technique enables individual, unbiased expression, is economical, easy to understand, and relatively simple to conduct.

If consensus cannot be reached by the Delphi technique, the panel is convened and group consensus techniques are utilized. The strengths and weaknesses of each test or procedure are discussed and consensus reached whenever possible. If "No consensus" appears in the rating column, reasons for this decision are added to the comment sections.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

ACR Appropriateness Criteria®

Clinical Condition: Induction and Adjuvant Therapy for N2 Non-Small-Cell Lung Cancer

Variant 1: 62-year-old male with a good performance status with clinical T2N2M0 non-small-cell lung cancer. Candidate for lobectomy.

Treatment	Appropriateness Rating	Comments
Radiation therapy alone	2	
Surgery alone	2	

Treatment	Appropriateness Rating	Comments
Timing of Chemo With Radiation Therapy or Surgery—If Given		
Concurrent chemoradiation, then surgery	7	
Concurrent definitive chemoradiation; no surgery	7	Some patients are not surgical candidates. Refer to the Appropriateness Criteria® Nonsurgical, Aggressive Therapy for NSCLC topic.
Neoadjuvant chemotherapy, then surgery	6	Adjuvant chemotherapy +/- radiation therapy may be indicated depending on pathologic findings.
Sequential chemotherapy, then radiation, then surgery	4	
Local Irradiation Doses		
30 Gy/2 weeks	2	
40 Gy/4 weeks	2	
45 Gy/5 weeks	8	Preoperative
50 Gy/5 weeks	8	Postoperative
55 Gy/7-8 weeks (split course)	2	
60 Gy/6 weeks	8	Postoperative (gross residual tumor)
Radiotherapy Technique		
Multifield technique	9	
AP/PA only	6	
Computer planning	9	
CT-based planning	9	
Complex blocking	9	
Appropriateness Criteria Scale 1 2 3 4 5 6 7 8 9 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 2: 62-year-old male with a good performance status with clinical T2N2M0 Non-Small-Cell Lung Cancer. Right pneumonectomy planned.

Treatment	Appropriateness Rating	Comments
Radiation therapy alone	2	
Surgery alone	2	
Timing of Chemo With Radiation Therapy or Surgery—If Given		
Neoadjuvant chemotherapy, then surgery	7	Adjuvant chemotherapy +/- radiation therapy may be indicated depending on pathologic findings
Concurrent definitive chemoradiation, no surgery	7	Some patients are not surgical candidates. Refer to the Appropriateness Criteria® Nonsurgical, Aggressive Therapy for NSCLC topic.
Concurrent chemoradiation, then surgery	2	May be more appropriate, if LEFT pneumonectomy contemplated.
Sequential chemotherapy, then radiation, then surgery	2	
Local Irradiation Doses		
30 Gy/2 weeks	2	
40 Gy/4 weeks	2	
45 Gy/5 weeks	8	Preoperative
50 Gy/5 weeks	8	Postoperative
55 Gy/7-8 weeks (split course)	2	
60 Gy/6 weeks	8	Postoperative (gross residual tumor)
Radiotherapy Technique		
Multifield technique	9	
AP/PA only	6	

Treatment	Appropriateness Rating	Comments
Computer planning	9	
CT-based planning	9	
Complex blocking	9	
Appropriateness Criteria Scale 1 2 3 4 5 6 7 8 9 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Introduction

Only 20% of patients with non-small-cell lung cancer (NSCLC) present with early-stage disease (American Joint Committee on Cancer [AJCC] clinical stage I and II), which is traditionally treated with surgical resection alone. The results of the International Adjuvant Lung Cancer Trial study, among others, make a case for adjuvant treatment even in these early-stage patients. The situation with regard to stage III patients is much more complicated. Stage III is heterogeneous. Patients with T3N1 tumors have a better prognosis than those with N2 nodes. In the latter group the risk of distant metastases is higher, and it is also more difficult to achieve local control. Within the stage III grouping, patient presentation also affects management. Several distinct subgroups of patients are identifiable:

- Some patients are initially considered to have stage I, II, or IIIA (but N1) disease and are upstaged at surgery (e.g., those with T3N0-1 disease with no evidence of mediastinal involvement on preoperative studies, including mediastinoscopy, who are found to have positive N2 nodes [ipsilateral mediastinal] at thoracotomy).
- Another subset of stage III patients are those with more locally advanced N2 disease, detected by clinical staging or mediastinoscopy. Some of them may be judged to be operable at presentation and some inoperable.
- Stage IIIB patients without N3 nodes, but with T4 primary tumors present particular local control challenges
- Finally, there are stage III patients with minimal N2 disease who, though surgically resectable, are medically inoperable and for this reason are treated with nonsurgical therapies.

The published literature is confusing because study populations contain individuals from each of these different groups, making it difficult to compare results across studies. Evaluation of the reported trials is further complicated by vague, variable, and sometimes absent definitions of what is meant by "unresectable," "marginally resectable," or "locally advanced." Changes in the staging system and the failure to clarify patient performance characteristics in many of the trials also make comparisons difficult. The trials also differ in the method of documentation of N2 status (radiographic vs histologic), by which patients undergo surgery (those with stable disease or those with responding tumors), and in their definition of a complete resection (removal of gross disease vs complete resection with negative margins). Definition of what is meant by "bulky" N2 disease has also varied. In some trials, it meant the presence of a single N2 node with intranodal involvement; in some other trials, it involved nodal stations N5 or N6 only; and in others, it involved positive N7 nodes. Finally, in some of the surgical trials, resection and survival rate were stated only for those undergoing thoractomy, and did not include those who received preoperative treatment and were unable, for various reasons, to go to surgery.

We will evaluate the published data as it pertains to NSCLC patients with N2 disease to evaluate the individual roles of surgery, radiation therapy, and chemotherapy. As we do so, we must keep in mind the wide variations in presentation in this very heterogeneous patient group. The published studies often include patients with both less (stages I, II, and N1) and more (N3, stage IV) advanced disease, mixed with the population of interest to the present discussion. Biologically, the difference between N2 patients and the earlier stages is that 1) the risk of metastatic failure is greater and therefore the corresponding benefit of systemic adjuvant therapy is also likely to be greater, and 2) local control is more problematic, so that surgery is not guaranteed to prevent local failure. It is unlikely that N2 (mediastinal) adenopathy is curable by surgery alone. On the other hand, this is probably true of N1 nodal disease. Therefore, the surgical data from lower stages must be interpreted and generalized with caution. The difference between the N2 patient group and more advanced presentations is that in the latter the risk of metastases is overwhelming, so the greatest therapeutic benefit is likely to come from systemic treatment. In patients with N2 disease, on the other hand, the risks of both local and distant failure are comparable, so that local and systemic treatment modalities may contribute to a similar degree.

Broadly speaking, some patients with N2 disease are candidates for surgery and some are not. It is not clear that all patients who are surgical candidates actually benefit from surgery, but what has become clear is that even operated-on patients benefit from additional treatment. We will evaluate the roles of surgery, radiation therapy (RT), and chemotherapy in this setting. In patients who are not surgical candidates at all, the roles of chemotherapy and RT and sequencing issues will be reviewed. The issues with regard to surgical patients discussed below are: 1) Do patients incidentally found to have N2 disease at surgery benefit from additional treatment? 2) Do resectable patients with clinically detected N2 nodes benefit from neoadjuvant treatment? 3) Does this same group benefit from adjuvant treatment? 4) Do borderline or unresectable patients benefit from neoadjuvant treatment administered with the goal of making them resectable? 5) Would this latter group do as well or even better with nonoperative treatment?

Results of Radiation Therapy Alone

The overall long-term survival rate for patients with clinical N2 disease treated with conventionally fractionated RT alone is a small, but finite—5%-10% at 5 years—and is viewed as largely inadequate. Although patients with N2 disease who are treated with surgery appear to have better survival, it must be recognized that they frequently have smaller primary tumors (T1-2 vs T3-4), better performance status, and less pretreatment weight loss than patients selected for RT. Thus, the results of surgery and RT in this patient population are not directly comparable. Furthermore, these patients often receive postoperative RT anyway. The outcome of RT alone vs surgery alone for similarly selected N2 patients has never been tested in a Phase III comparison trial. The potential results of RT alone delivered to the subset of N2 patients felt suitable for surgery are not clearly known. In a discussion of this issue, one set of researchers reports a 7% 3-year survival rate after standard fractionation RT alone for N2 patients with Karnofsky Performance Score of 70-100, < 5% weight loss, and with similar T stage distribution as in surgical series. For hyperfractionated RT alone to 69.6 Gy, tested in a Phase II trial of patients with IIIA/B disease, the 3-year survival rate for the IIIA (N2) patients was 20%.

Hyperfractionation to 69.6 Gy was compared to standard fractionation to 60 Gy and to induction chemotherapy (cisplatin and vinblastine) followed by RT to 60 Gy in 6 weeks in a three-arm Phase III Radiation Therapy Oncology Group® (RTOG®) 8808 intergroup trial. Just over half of the 452 patients entered had N2 disease. For the entire group, the median survival time and 1-year survival rate for the standard RT arm (11.4 months; 46%) were not significantly different from the hyperfractionation arm (12.3 months; 51%). Median survival time (13.8 months) and 1-year survival rate (60%) were significantly better for the chemotherapy/RT arm than for the standard or hyperfractionated RT arms. The addition of chemotherapy to radiation therapy is discussed under a separate heading below.

An even more aggressive thrice-daily hyperfractionation schedule to 54 Gy in 12 days of continuous hyperfractionated accelerated radiation treatment (CHART) was compared by the Medical Research Council of the United Kingdom to standard RT to 60 Gy and showed a distinct survival advantage. One-year survival rate improved from 55% to 63%. The 2-year survival rate increased from 20% to 29%, and the improvement was linked to a decrease in local recurrence. There was no increase in late toxicity, although acute toxicity was significantly increased.

Other forms of RT alone, such as neutron irradiation and both interstitial and endobronchial brachytherapy, have been tested, but with no clear-cut advantage noted for either approach. Neutrons (20.4 nGy/4 weeks) were compared to photons (66 Gy/7 weeks) in a Phase III trial of 200 patients with inoperable stage III NSCLC. The median survival time (9.7 months) and 2-year survival rate (14%) for neutron therapy were not different than those for photon therapy (8.9 months; 10%). In fact, the outcomes in both arms seem somewhat worse than the photon data reported by other authors. Brachytherapy has been used as a boost to local tumor following external beam RT, both in the form of interstitial implants and as endobronchial sources. Neither treatment has been tested in a controlled fashion, nor has N2 disease been the focus of these trials, and existing data do not suggest a distinct advantage for either over external beam therapy alone.

In general, distant metastatic failure is the dominant pattern of failure in this patient population. Therefore, the addition of systemic therapy has become the focus of ongoing studies. For the same reason, adjuvant treatment is being evaluated in combination with surgery, which is also a purely local treatment.

Results of Surgery Alone

The argument in favor of surgery is based on the assumption that surgery results in better local control of primary disease than does RT. While this is likely true for early NSCLC, it is unproven for patients with N2 cancers. As discussed above there are uncertainties about the total population from which the surgical patients were drawn, compared to the RT population, with regard to smaller primary tumors, better performance status, less pretreatment weight loss, etc. Also, most studies in the literature have used postoperative RT when indicated in selected patients. This further complicates the interpretation of the role of surgery for N2 disease. The collective 5-year survival rates of surgery alone for stage III (N2) disease range from 14%-30%. Despite negative preoperative staging, including mediastinoscopy, approximately one-fourth of patients felt to be T1-3N0-1 may have occult N2 disease. The increased use of positron emission tomography (PET) scanning may, however, improve preoperative staging. PET is more sensitive and specific at mediastinal nodal staging than CT, and an improved ability to assess mediastinal nodal involvement has important patient management implications. Approximately 12%-15% of the resected patients will have T1 disease, 45% T2 disease, and 40% T3 disease. Incomplete resection rarely results in long-term survival. Several factors predict a poor prognosis: preoperatively identified N2 disease, multiple involved lymph nodes or sites, bulky extracapsular disease, T3 tumors, and nonsquamous histology. The benefit of surgery in these patients is questionable. Thus, preoperative staging that identifies these features suggests a marginally resectable situation. These patients are also referred to as having "bulky" N2 disease or "locally advanced disease." Patients with N2 disease and less advanced primaries and squamous histology may have a better prognosis.

A direct comparison of the roles of surgery and radiation therapy in similar patients has been attempted. The RTOG® 89-01 randomized study was designed to compare induction chemotherapy followed by surgery vs. RT in stage IIIA patients with pathologically documented N2 nodes. Unfortunately, the study accrued poorly, and only 45 patients were randomized. With this small number of patients there was no difference in 1-year survival rate (70% vs. 66%) or median survival time (19.4 months vs. 17.4 months) between the surgery and RT arms. The subsequent RTOG® 93-09 study (discussed in greater detail below) was designed to address the role of surgery in combined modality therapy. Patients with T1-3, pN2, M0 tumors were eligible if resection was technically feasible at registration. A total of 429 randomized patients received induction chemotherapy and daily RT to 45 Gy starting on day one. Arm 1 then had resection if there was no progression, followed by two more chemotherapy cycles. Arm 2 had uninterrupted RT to 61 Gy with two more cycles of chemotherapy. It appears that surgery was associated with higher up-front mortality, but with more late survivors. The overall survival time curves cross at the median (which is the same; Arm 1, 22.1 months; Arm 2, 21.7 months), so that by year 3 there is a trend towards better survival with surgery (38% vs. 33%; p=NS). With longer follow-up the surgery arm may show superior survival, but median survival is the same. This raises the question of how to balance a greater number of early deaths against better outcomes in patients who do survive beyond treatment.

Preoperative or Postoperative Radiation Therapy

Randomized trials have failed to show a survival benefit when preoperative RT was compared to surgery alone, but many of the trials are fairly old, and modern noninvasive and intraoperative staging techniques were not used. In a more recent trial of the Lung Cancer Study Group (LCSG 881) patients received either preoperative RT to 44 Gy or preoperative cisplatin, mitomycin and vinblastine in a randomized Phase II trial of patients with pathologically proven stage IIIA disease. However, median survival time was only 12 months, and a pathologic complete response (CR) was seen in only 2 of 57 patients (1 in each arm) patients. Despite more modern methods, preoperative RT does not appear to increase survival.

Despite evidence of improved local control from Phase II and III trials of RT following surgery compared to surgery alone, no survival benefit has ever been documented for patients with stage IIIA disease. A Phase III trial of postoperative RT conducted by the LCSG showed a significant reduction in local recurrences, but no survival benefit. Although the trial is considered to have provided the best available data, it had several design flaws and operational problems. Thus, many oncologists feel a truly definitive Phase III trial of postoperative RT has not yet been done. The meta-analysis of postoperative RT included many older studies in which patients with stage I and II disease, who are not considered candidates for postoperative RT in contemporary practice, nevertheless received RT. These patients suffered a detriment. The role of postoperative RT in N2 patients was not clarified by this study. In a study of 173 postoperatively irradiated patients, locoregional control for stage IIIA was 85%, and 5-year actuarial survival rate was 20%. In a regression-tree analysis of recurrence risks, patients with N2 nodes who underwent gross resection were at a high risk for local recurrence and were thought to be likely to benefit from postoperative RT. In 1997, the Canadian Lung Cancer Disease Site Group (CLCDSG) published a practice guideline for postoperative RT for stage IIIA NSCLC, stating that the evidence available suggests RT reduces the local recurrence rate by 18% in completely resected stage IIIA NSCLC. For this reason, the CLCDSG recommended postoperative RT but also concluded that there was no evidence of a survival benefit from postoperative RT alone. As stated previously, many patients in surgical series have received postoperative RT as well.

Most authors feel that failure to show a survival benefit for postoperative RT is due to systemic disease progression, a problem not directly addressed by RT. An intergroup trial for resected stage II-IIIA NSCLC failed to show a survival difference between postoperative RT alone and postoperative concurrent platinum-based chemotherapy and RT. Unfortunately, this trial result still does not clarify the question of whether the postoperative RT contributed a survival benefit.

Combined Modality Treatment with Surgery

The results of surgical series appear superior to those of RT series. As discussed above, much of this difference can be attributed to patient selection, and no satisfactory direct comparison of surgical and nonsurgical treatment in a randomized setting has been performed. Since there is a perception that the results of surgery are superior, combined modality approaches aim to incorporate surgery into treatment. Two strategies have been commonly employed. One is to convert inoperable and marginally operable patients to operability by some combination of preoperative chemotherapy and RT. The other is to improve on the results of surgery in patients deemed to be operable at presentation by the addition of adjuvant chemotherapy or RT or both. Clearly, the morbidity of trimodality therapy is considerable, and it is still uncertain whether in N2 disease, where the risk of distant failure is large, and local control is not guaranteed by surgery, the benefits of a strictly local treatment like surgery are superior to those of chemoradiation alone.

The majority of studies fall into one of two categories: those using surgical approaches (with adjuvant or neoadjuvant combinations of chemotherapy and radiation therapy), and nonsurgical trials of definitive chemoradiation. We will next consider the surgical trials.

Surgery after Neoadjuvant Chemotherapy

Numerous Phase I/II and retrospective studies have addressed the use of induction chemotherapy before surgery in patients with stage IIIA/B disease. These studies established the safety of doing surgery after induction chemotherapy. In some of these studies postoperative RT was given to some patients, and some lower stage patients were also included. Response rates to induction chemotherapy were in the 40%-74% range, with a few complete responders. Good responses correlated with favorable outcomes. Median survival time ranged from 15 to 33 months, and long-term survival rates were 22%-40%. In responding patients, median survival times were in the 26-month range and long-term survival rates were as high as 55%.

There is less information about patients who had poor responses or could not be completely resected, but in this situation median survival times appears much lower (8 months in one study). The CLCDSG reviewed the literature with respect to the benefit of preoperative chemotherapy with or without postoperative RT and concluded that there is evidence from relatively small clinical trials that survival is better compared to surgery and postoperative RT. They recommended that in cases where surgery is planned in patients with histologically confirmed N2 disease, preoperative chemotherapy and postoperative RT should be offered. Neoadjuvant chemotherapy recently received a large boost from the Bimodality Lung Oncology Team (BLOT) study in which carboplatin and paclitaxel were administered to mediastinal node-negative patients (documented by mediastinoscopy) both preoperatively and postoperatively. The 3-year survival rate was 61%.

The existing Phase III randomized data with this approach are contradictory. A French study randomized 355 resectable stage I (except T1N0), II, and IIIA patients to either preoperative chemotherapy (cisplatin, mitomycin, and ifosfamide for two cycles; two additional cycles postoperatively for responders); or surgery alone. Postoperative RT was given to patients with pT3 or pN2 disease. Median survival time was 37 months for the chemotherapy group compared to 26 months in the surgery alone group (p=NS). There was a survival benefit confined to stage I and II patients. On the other hand, in a randomized study, 60 patients were randomized to similar preoperative chemotherapy with cisplatin, ifosfamide, and mitomycin, given for three cycles every 3 weeks preoperatively, or to surgery alone. Median survival time was 26 months in the chemotherapy group compared to 8 months for surgery alone ($p < 0.001$). Similarly, in another study, patients were randomized to six cycles of perioperative cisplatin, etoposide, and cyclophosphamide or to surgery alone. The median survival time in the chemotherapy arm was 64 months compared to 11 months in the surgery alone arm ($p < 0.008$).

These trials have been much discussed, and the results have been somewhat controversial because of their strongly positive results favoring adjuvant chemotherapy and the small number of patients (60) in both trials. Also N2 involvement was not required, and mediastinoscopy was not mandated if the mediastinum was negative by computed tomography. One trial had 40% stage IIIB and IV patients in the surgery-only arm, leading to speculation that stage maldistribution between the two arms was skewed in favor of the chemotherapy arm. In contrast, the other trial had unexpectedly low survival rates (0% at 3 years) in the surgery alone arm, even though 37% had only N0 or N1 disease. Other factors, such as undetected imbalances in one or several prognostic factors between study arms for the two trials, may also explain the observed differences.

The role of surgery in the setting of neoadjuvant chemotherapy was evaluated by the RTOG® 89-01 study. Induction chemotherapy (cisplatin, vinblastine, and mitomycin C, with mitomycin dropped part way through the study) was followed by either surgery or RT in stage IIIA patients with pathologically documented N2 nodes. Unfortunately, the study accrued poorly, and only 45 patients were randomized. With this small number of patients there was no difference in 1-year survival rates (70% vs. 66%) or median survival time (19.4 vs. 17.4 months) between the surgery and RT arms.

Similarly, the EORTC 08941 study compared radical surgery with thoracic radiotherapy following 3 cycles of platinum-based induction chemotherapy in selected patients with stage IIIA-N2 NSCLC. Responding patients were randomized between radical resection with lymph node dissection and optional postoperative RT, and thoracic RT (at least 40 Gy in 2 Gy daily fractions to the mediastinum with a boost to at least 60 Gy). Three hundred thirty-three patients were randomized. One hundred fifty-four patients actually had surgery and 155 had radiation. Operative mortality was 4% and 39% received post operative RT. With a median follow up of 72 months, median 2-year and 5-year overall survival (OS) for patients randomized to surgery compared to radiation therapy were 16.4 and 17.5 months, 35% vs. 41% and 16% vs. 13%, respectively (HR 0. 95, 95% CI 0.75-1.19). Median and 2-year progressive free survival for patients randomized to surgery and radiation were 9.0 months vs. 11.4 months and 27% vs. 24%, respectively ($p=0.6$). It was concluded that in patients with a response to induction chemotherapy, surgery improves neither OS nor progression-free survival (PFS) as compared to thoracic radiation. These results are interesting in the context of the RTOG® 93-09 study which used induction chemoradiation (discussed below).

Surgery after Neoadjuvant Chemoradiotherapy

The survival benefit of reducing distant failure by adding chemotherapy to RT as demonstrated in randomized Phase III trials for inoperable NSCLC stimulated interest in preoperative treatment with RT and chemotherapy instead of either RT or chemotherapy alone. The objective of these trials was to use the RT, aided by chemotherapy radiosensitization, to shrink the primary tumor and bulky N2 disease, the chemotherapy to sterilize distant micrometastases, and surgery to optimize local control by removal of residual tumor.

A Southwest Oncology Group (SWOG) study demonstrated the feasibility of surgery after two cycles of preoperative cisplatin and etoposide and RT (45 Gy) in patients with stage IIIA/B NSCLC. Resectability rates for stage IIIA and IIIB patients were 85% and 80%, respectively, and 2-year survival rates were 27% and 24%, respectively. Subsequently, numerous Phase I/II and retrospective studies have investigated different neoadjuvant chemotherapy and RT combinations. These studies have demonstrated the safety and feasibility of this approach, although there is an indication of higher operative morbidity than without neoadjuvant treatment. Outcomes are variably reported, and the studies tend to focus on patients who were able to be resected, with less information regarding the outcomes of patients unable to have surgery. Response rates (complete plus partial) to induction therapy ranged from 42% to 93%. Median survival times ranged from 11 to 52 months, and long-term overall survival rates were in the 11%-56% range. In general, good responses to neoadjuvant treatment (variously defined as complete response, only microscopic residual disease, N2 nodes converted to negativity, etc.) were associated with a significantly better outcome (median survival times 35-36 months, long-term overall survival rates 48%-54%) compared to poor responders (median survival times 11-14 months, long-term survival rates 9%-24%). It appears from these data that many major responders are cured. Their likely outcome with definitive chemoradiation without surgery is unknown. On the other hand, it appears that few poor responders are cured by surgery following induction therapy.

A German Phase III study of stage IIIA/B NSCLC randomized 558 patients to preoperative chemotherapy (cisplatin/etoposide) followed by concurrent hyperfractionated chemoradiation (45 Gy; 2 x 1.5 Gy/day with carboplatin and vindesin) or to preoperative cisplatin/etoposide alone. Both arms then went to surgery. After surgery, patients in the induction concurrent chemoradiation arm received postoperative RT only if they had less than an R1/2 resection, while all patients in the induction chemotherapy alone arm received postoperative RT. There were no survival differences (3-year survival rates: 24% vs 23%; p=0.89). However, all patients did receive RT, either preoperatively or postoperatively, so this study did not really address the role of RT in the surgical setting. On the other hand, there was also no difference in response or resectability rates between the two arms, suggesting that the addition of preoperative RT to chemotherapy did not contribute to outcomes.

The phase III RTOG 93-09 study was designed to address the role of surgery in combined modality therapy. Patients with T1-3, pN2, M0 tumors were eligible if resection was technically feasible at registration. A total of 429 randomized patients received induction with cisplatin and etoposide for 2 cycles and daily RT to 45 Gy starting on day 1. Arm 1 then had a resection if there was no progression, followed by two more chemotherapy cycles. Arm 2 had uninterrupted RT to 61 Gy with 2 more cycles of chemotherapy. The trial accrued slowly but was closed with sufficient events. It has only been reported in abstract at this time. It appears that surgery was associated with higher up-front mortality, but with more late survivors. There were more early non-cancer deaths in the surgery arm, but the overall survival curves crossed at the median (Arm 1, 22.1 months; Arm 2, 21.7 months), so that by year 3 there was a trend towards better survival with surgery (38% vs. 33%; p=NS). More deaths occurred during treatment on Arm 1 (15 vs. 3). Fourteen of the 15 deaths occurred in patients who had a pneumonectomy, with most being right pneumonectomies. More patients were alive without progression on Arm 1 (p=.003), but more died without progression (p=.004). Progression-free survival was superior on Arm 1 (log-rank p=.02): median, 14.0 vs. 11.7 months; 3-year survival rate 29% vs. 19%.

With longer follow-up the surgery arm may have shown superior survival, but median survival was the same and this raises the question of how to balance a greater number of early deaths against better outcomes in patients who survive beyond treatment. It is possible that better surgical technique can reduce operative morbidity and mortality and that centers with more experience with combined modality therapy would have fewer treatment-related deaths. Patient selection also appears critical to the success of this trimodality strategy. All the deaths in the operative arm were treated by pneumonectomy after induction chemoradiation, but patients who were treated by a lobectomy tolerated this treatment regimen with less toxicity. The decision regarding resectability of tumors is critical and obviously highly individualized. Clearly, studies enroll patients with the best performance status and minimal weight loss. For all these reasons it is unclear how to generalize the results of this study to the care of average patients, both at tertiary referral centers and in the community.

Postoperative Chemotherapy

The CLCDSG concluded from a review of the early literature that postoperative chemotherapy, with or without RT, resulted in slight reduction (not statistically significant) in the risk of death in resected stage IIIA NSCLC. A large randomized study of postoperative chemotherapy (cisplatin and etoposide) concurrent with RT (50.4 Gy) compared with the same RT alone found no difference in overall or recurrence-free survival time (median survival times: 38 months and 39 months, respectively). A meta-analysis of the benefits of postoperative chemotherapy (mainly alkylating agents) showed no benefit from this approach. However, the subset of patients who received cisplatin appeared to have a 5% higher 5-year survival rate, although the total number of such patients was small and the p value was not significant at 0.08. A large, randomized Italian trial from the Adjuvant Lung Project Italy (ALPI) used mitomycin, vindesine, and cisplatin as adjuvant treatment in stage I-III NSCLC. The use of postoperative RT was at the discretion of the treating institution, and it was given to the majority of patients in each arm. No overall survival or progression-free survival benefit was observed.

On the other hand, the International Adjuvant Lung Cancer Trial (IALT) found a significant difference in overall survival rates (45% vs. 40% at 5 years; p <0.03) in favor of patients treated with adjuvant cisplatin-containing chemotherapy compared to observation. The study included stage I-III patients and postoperative RT and was administered at the discretion of the treating institution. A randomized Japanese trial of stage I patients also showed a survival benefit in favor of postoperative uracil/tegafur (UFT) compared to surgery alone, although the difference was small (88% vs 85%, p=0.036). A study from the National Cancer Institute of Canada (Intergroup JBR 10) of stage IB and II patients randomized between adjuvant vinorelbine and cisplatin or observation. Overall survival was significantly prolonged in the chemotherapy group as compared with the observation group (94 vs. 73 months; hazard ratio for death, 0.69; =0.04), as was relapse-free survival (not reached vs. 46.7 months; hazard ratio for recurrence, 0.60; P<0.001). Five-year survival rates were 69% and 54% respectively (=0.03). CALGB Protocol 9633 of stage IB patients, currently only reported in abstract, showed a significant benefit from adjuvant chemotherapy of stage IB patients. There was a significant advantage in failure-free survival favoring the chemotherapy group (HR=0.69; 95% CI: 0.48-0.98; p=0.035). With regard to lung cancer mortality, there have been 19 lung cancer deaths in the chemotherapy group and 34 deaths in the control group (HR=0.51; 95% CI: 0.29-0.89; p=0.018).

The Adjuvant Navelbine International Trialist Association (ANITA) study compared the effectiveness of adjuvant vinorelbine and cisplatin for 4 cycles to observation in Stage I, II and III NSCLC. Completely resected patients were randomized and radiotherapy policy was not reported, other than that it was predetermined by each center. Eight hundred forty patients at 101 centers were randomized. With median follow-up greater than 70 months, median survival was 65.8 months in the adjuvant chemotherapy group and 43.7 months in the observation group (P=0.0131; hazard ratio, 1.264 [1.05–1.52]). Five-year survival rates for stage I, II, IIIA patients were 62%, 52%, and 42%, respectively, for adjuvant chemotherapy and 63%, 39%, and 26%, respectively, for observation. It was concluded that adjuvant cisplatin and vinorelbine significantly improve survival in completely resected stage II and IIIA NSCLC patients, although no benefit was observed in stage I. The difficulty in interpreting all these studies resides in the great heterogeneity of patients, with the majority having early disease, particularly in the most positive studies.

Considerations Regarding Surgery with Adjuvant Treatment

The variations in stage, eligibility requirements, and lack of pathologic documentation of N2 status in the various studies described above account for the wide range of survival rates. It must be emphasized that these results only apply to good performance patients, since the trials restricted entry to patients with optimal treatment tolerance characteristics. It remains to be seen how less fit patients would tolerate such treatment and how treatment may have to be modified to retain tolerance. Also, no induction regimen can be identified as superior at this time, nor is there one chemotherapy combination that can be recommended, since no trials have attempted to test this.

There is evidence that 40%-93% of patients will respond to induction with chemotherapy with or without RT, that about half of the responders will go on to surgical resection, and that about 10% of all entered patients will have complete histologic clearance of tumor. Clearly, patients who have a good response do well. It is equally clear that patients with a poor response to neoadjuvant treatment do poorly. There is no way to predict which patients will have a good response. On the basis of existing studies, it is premature to draw final conclusions. There is, as yet, no conclusive evidence of benefit from adding of preoperative chemotherapy or chemotherapy and RT to surgery for N2 NSCLC. It appears premature to conclude that postinduction surgery should be the standard of care for patients with Stage IIIA (N2) NSCLC. Based on the existing evidence, as stated in the NCCN guidelines, surgery following chemotherapy with or without radiation may be an appropriate alternative to chemoradiation alone in this subset of patients. It appears appropriate in highly selected patients at centers with experience with this approach. It should not be applied routinely to patients with bulky N2 disease considered unresectable at presentation, as there is no evidence that trimodality therapy is of benefit in this setting. It is unclear whether RT added to chemotherapy in the preoperative setting contributes to survival, although response rates seem higher with the addition of RT. Despite earlier studies that showed no benefit, emerging evidence appears to support its use. While there is no evidence for a survival benefit to adjuvant RT for N2 disease, it has been widely used in the studies discussed and should therefore continue to be used pending evidence to the contrary.

Combined Radiation Therapy and Chemotherapy without Surgery

With the development of effective, cisplatin-based chemotherapy for NSCLC, numerous Phase II trials suggested an improvement in response rates and survival with the addition of chemotherapy, compared to the historical results with RT alone. Only the more recent ones are summarized in the evidence table in the original guideline document. Phase III randomized trials were then designed to address sequencing issues of RT and chemotherapy. In principle, chemotherapy can be administered, before, during, or after RT, or in any combination of these options.

Sequential Chemotherapy Followed by Radiation Therapy

Induction chemotherapy followed by RT was the first regimen explored in a rigorous fashion. Subsequent results have supported the relatively low toxicity of this approach, compared other regimens. The landmark CALGB 8433 study showed a two-fold increase in 7-year survival rates (13% vs. 6%) with the addition of two courses of induction chemotherapy to standard RT (60 Gy). These results were confirmed by studies in both Europe and the United States, and established sequential chemotherapy followed by RT as the standard treatment for unresectable NSCLC in good performance patients. Other groups from around the world have come to similar conclusions. Subsequent studies were designed to test concurrent chemotherapy and RT.

Concurrent Chemoradiation

A European Phase III randomized study compared split course RT alone to the same RT with two concurrent cisplatin regimens. Survival rate in the daily concurrent cisplatin arm was 16% at 3 years, compared to 2% in the RT alone arm. The especially poor result in the RT alone arm is perhaps not surprising in the context of split course RT. The Phase III Japanese study compared sequential chemotherapy and RT with concurrent chemotherapy and RT. Split course RT was used in the concurrent arm and daily RT in the sequential arm. Chemotherapy (mitomycin, vindesine, and cisplatin) was the same in both arms. This study showed significantly better short-term survival (median survival time 16.5 months vs 13.3 months) and long-term survival (5-year survival rates 15.8% vs 8.8%) for concurrent chemotherapy and split course RT compared to the same chemotherapy given as induction followed by standard RT. The chemotherapy doses were not reduced in the concurrent regimen. Apparently, the split course RT conferred some protection from chemotherapy-enhanced acute toxicity, since the rate of esophagitis was low in both groups.

The issue of sequencing of chemotherapy and RT in the context of more common U.S. chemotherapy and RT regimens was addressed by the recently completed three-arm Phase III RTOG® 94-10 trial, so far reported in abstract only. The three arms were: induction chemotherapy (cisplatin and vinblastine) followed by standard RT (60 Gy/6 weeks) as in the experimental arm of the CALGB 8433 study, concurrent chemotherapy (same agents) and standard RT (60 Gy/6 weeks), and concurrent chemotherapy (cisplatin and etoposide) with hyperfractionated RT (69.6 Gy/6 weeks). Median survival times were 14.6, 17, and 15.2 months for the three-arms, respectively. Four-year survival rates were 12%, 21%, and 17%, respectively. The concurrent chemotherapy with once daily RT arm had better survival than the sequential arm (p=0.046). The concurrent twice daily RT arm was not significantly better than the sequential arm. This result, while supporting the superiority of concurrent over sequential regimens, has reduced the enthusiasm for hyperfractionated RT, at least concurrently with chemotherapy.

The recently reported Czech Phase III randomized study compared induction cisplatin and vinorelbine followed by daily RT (60 Gy in 6 weeks) with the same chemotherapy administered concurrently with the same RT. Median survival time was better (16.6 months vs 12.9 months; p=0.023) in the concurrent chemotherapy and RT arm. Response rates and time to progression were also significantly better.

Other studies also support the superiority of concurrent over sequential regimens. The study of the German BROCAT group compared sequential carboplatin and paclitaxel chemotherapy followed by RT (60 Gy) to the same induction regimen followed by concurrent weekly paclitaxel and the same RT. A recent abstract reports median survival time of 18.67 months compared to 14.1 months in the sequential arm. The French GLOT study reported on sequential chemotherapy (cisplatin and vinorelbine, followed by 66 Gy of thoracic RT) compared with concurrent RT with cisplatin and etoposide, followed by cisplatin and vinorelbine. Median survival time was 13.8 months in the sequential arm compared to 15 months in the concurrent arm (p=NS).

These studies have been influential in establishing concurrent chemoradiation as the new standard for locally advanced NSCLC in good performance patients.

Induction Chemotherapy Followed by Concurrent Chemoradiation

After studies showed the superiority of concurrent chemotherapy and RT regimens over sequential regimens, there has been considerable interest in adding induction chemotherapy to concurrent chemoradiation. The Cancer and Leukemia Group B (CALGB) 39801 Phase III randomized study compared concurrent chemotherapy with RT (carboplatin and paclitaxel; 66 Gy) with the same regimen preceded by two cycles of induction carboplatin and paclitaxel in unresectable stage III patients. The results of the study have recently been reported in abstract form. A total of 366 patients were randomized. Median survival time was 11.4 months (p=0.154) in the concurrent arm compared to and 14 months in the induction plus concurrent arm. The one-year survival rate was 48% vs. 54%. The differences are not statistically significant.

The Locally Advanced Multimodality Protocol (LAMP) study enrolled unresectable stage IIIA/B patients and also used carboplatin and paclitaxel and had three arms: two cycles of chemotherapy followed by 63 Gy of thoracic RT (sequential), two cycles of induction chemotherapy followed by concurrent chemotherapy, and RT (induction/concurrent) and concurrent chemotherapy and RT followed by two cycles of consolidation chemotherapy (concurrent/consolidation). An abstract reports that median survival times were 12.5, 11, and 16.1 months, respectively, with a median follow-up of 26 months. The mature data from this study will shed more light on the question of adding more chemotherapy to concurrent chemoradiation.

These two studies discussed above imply that induction chemotherapy followed by concurrent chemoradiation cannot be recommended as standard treatment at the present time. The role of consolidation chemotherapy following concurrent chemoradiation needs further evaluation, but it appears more promising. In addition to the preliminary Phase III data from the LAMP study above, the Southwest Oncology Group (SWOG) S9504 Phase II study reported a median survival time of 26 months and a 3-year survival rate of 37% for 83 stage IIIB patients treated with cisplatin and etoposide concurrent with 61 Gy of thoracic RT followed by consolidation docetaxel. A Hoosier Oncology Group (HOG) study is also investigating the role of consolidation chemotherapy after concurrent chemoradiation. Future studies will shed more light on the question.

Conclusions

Surgical series of patients considered operable at presentation show good survival. Even if this is secondary to patient selection, given the state of the data, these patients should go to surgery. The patients with the best results after surgery are those with cT3N0-1 disease, with no evidence of mediastinal disease on preoperative studies, including mediastinoscopy, who are found to have N2 nodes at thoractomy. Adjuvant treatment is indicated. Postoperative RT has been extensively used for N2 nodes and positive margins in the published studies, and the effect of RT must therefore be considered as incorporated into the study outcomes. Therefore, even absent proof of a survival benefit from postoperative RT, it should continue to be used pending additional study results. Despite earlier negative results with adjuvant chemotherapy, recent studies appear to show a benefit, particularly in early stage patients. Induction chemotherapy, with or without RT, is feasible. There are some data to support a benefit to neoadjuvant chemotherapy, but very little to support neoadjuvant chemoradiation. Toxicity concerns are real and it may be better to reserve RT for the postoperative setting when the final, postinduction pathologic extent of disease is known. Clearly, patients who respond poorly to induction therapy and still have N2 nodal positivity at surgery have poor outcomes, even with surgery. This may reflect the biology of their disease or a lack of benefit from surgery in this setting. There is as yet no way to predict which patients will respond and which will not. There are no data to support attempts to convert unresectable tumors to operability with neoadjuvant regimens, and this approach cannot be recommended at this time, outside of a protocol setting. Trimodality therapy consisting of neoadjuvant chemoradiation followed by surgery is associated with significant mortality, particularly after right pneumonectomy, and these patients may have the same outcome without surgery. If attempted, this form of treatment is best restricted to centers with experience with this approach.

Patients considered surgically unresectable or medically inoperable can be treated with chemotherapy and RT. Conventional thoracic RT alone, previously considered the standard of care for N2 patients, is no longer standard. RT alone remains a reasonable option for N2 patients with less favorable performance characteristics, who are poor candidates for the more aggressive combined modality approaches. Alternatively, these patients may be treated with sequential chemotherapy followed by RT. For patients with a good performance status, mounting evidence supports the use of concurrent chemoradiation. The addition of induction chemotherapy to concurrent chemoradiation cannot be recommended at this time. Adjuvant chemotherapy following concurrent chemoradiation cannot be recommended as standard, although promising early data suggest that this is a good strategy for investigation. Enrollment in protocols is encouraged.

New chemotherapy agents, novel RT approaches, and advanced surgical techniques will continue to be subjects of future research.

Abbreviations

- AP/PA, anterior-posterior/posterior-anterior
- CT, computed tomography

CLINICAL ALGORITHM(S)

Algorithms were not developed from criteria guidelines.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are based on analysis of the current literature and expert panel consensus.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Selection of appropriate radiologic procedures for management of patients with N2 non-small-cell lung cancer

POTENTIAL HARMS

- Trimodality therapy consisting of neoadjuvant chemoradiation followed by surgery was associated with higher operative morbidity and significant mortality, particularly after right pneumonectomy, and these patients may have the same outcome without surgery. If attempted, this form of treatment is best restricted to centers with experience with this approach.
- Thrice-daily hyperfractionation schedule to 54 Gy in 12 days of continuous hyperfractionated accelerated radiation treatment (CHART) was associated with increased acute toxicity as compared to standard radiation therapy (RT) to 60 Gy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

An American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those exams generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Gopal RS, Komaki RU, Bradley J, Gewanter RM, Movsas B, Rosenzweig KE, Thoms WW Jr, Weisenburger TH, Wolkov HB, Kaiser LR, Schiller JH, Mauch PM, Expert Panel on Radiation Oncology-Lung Work Group. Induction and adjuvant therapy for N2 non-small-cell lung cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2006. 16 p. [94 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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GUIDELINE DEVELOPER(S)

American College of Radiology - Medical Specialty Society

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GUIDELINE COMMITTEE

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology–Lung Work Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Byhardt RW, Sause WT, Curran WJ, Fuller D, Graham MV, Ko B, Komaki R, Weisenburger TH, Kaiser LR, Leibel SA,

Choi NC. Neoadjuvant therapy for marginally resectable (clinical N2), non-small cell lung cancer. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000 Jun;215(Suppl):1331-45.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

ACR Appropriateness Criteria® Anytime, Anywhere™ (PDA application). Available from the ACR Web site.

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- ACR Appropriateness Criteria®. Background and development. Reston (VA): American College of Radiology; 2 p. Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

PATIENT RESOURCES

None available

NGC STATUS

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